REMARKS

Claims 1, 2, and 4 to 7 are pending in the application. Claims 1 and 5 have been amended herein, without prejudice, to remove non-elected subject matter. No claims have been added or canceled. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

A. Claims 1, 3 to 5, and 7 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Mellor, H.R., *et al.*, *Analytical Biochemistry* 284:136-142 (2000) (hereinafter "the Mellor article"). The Office Action asserts that the compounds defined by the present claims are obvious variants of (2S,3R,4R,5S) 1-butyl-2-(hydroxymethyl)-3,4,5-piperidinetriol (N-butyl-idonojirimycin), shown in Table 1 on page 139 of the Mellor article, and the subject of proviso (a) of original claim 1. Applicants respectfully traverse the rejection because the N-butyl-idonojirimycin compound described in the Mellor article fails to render the claimed compounds *prima facie* obvious.

It is well settled law that "[i]f the prior art does not teach *any* specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds." M.P.E.P. § 2144.09 (citing *In re Stemniski*, 444, F.2d 581, 170 U.S.P.A. 342 (C.C.P.A. 1971)).

The Mellor article fails to describe or even suggest any specific or significant utility for N-butyl-idonojirimycin. Accordingly, Applicants respectfully submit that those skilled in the art would not have been motivated to make compounds structurally similar to N-butyl-idonojirimycin because there would have been no expectation of producing compounds useful as modulators of human glucosylceramide synthase (GCS). The Mellor article, therefore, fails to render compounds structurally similar to N-butyl-idonojirimycin *prima facie* obvious. Applicants accordingly, respectfully request withdrawal of the rejection.

B. Claims 1 to 7 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over published PCT application number WO 01/10429 (hereinafter "the Zitzmann

application"). The Office Action asserts that the compounds defined by the present claims are obvious variants of (2S,3S,4R,5S) 1-nonyl-2-(hydroxymethyl)-3,4,5-piperidinetriol (N-nonyl-altrostatin), shown in Figure 1 of the Zitzmann application, and the subject of proviso (c) of original claim 1, which is proviso (b) of claim 1 as amended herein. Applicants respectfully traverse the rejection because the N-nonyl-altrostatin compound described in the Zitzmann application fails to render the claimed compounds *prima facie* obvious.

The Zitzmann application fails to describe any significant utility for N-nonyl-altrostatin. Although the application describes experiments in which the anti-bovine viral diarrhea virus activity of N-nonyl-altrostatin was measured, N-nonyl-altrostatin failed to exhibit any significant anti-viral activity (Figure 5).[1] Accordingly, as with the Mellor article, Applicants respectfully submit that those skilled in the art would not have been motivated to make compounds structurally similar to N-nonyl-altrostatin as there would have been no expectation of producing compounds useful as modulators of GCS. The Zitzmann application, therefore, fails to render compounds structurally similar to N-nonyl-altrostatin *prima facie* obvious. Applicants accordingly, respectfully request withdrawal of the rejection.

C. The rejection of claims 1 to 7 under 35 U.S.C. § 103(a) as allegedly obvious over the Mellor article has been maintained for the reasons stated in the previous Office Action (dated August 24, 2004). Specifically, the August 24, 2004 Office Action asserts that, since several piperidine polyhydroxy compounds having various stereochemical configurations are described in the Mellor article, piperidine polyhydroxy compounds having the 2S,3R,4R,5S configuration would have been obvious to those skilled in the art. Applicants respectfully traverse the rejection because the unexpected advantages of the compounds defined by the present claims were not known in the art at the time the invention was made.

Preliminarily, Applicants note that Table 1 on page 139 of the Mellor article depicts four polyhydroxypiperidine compounds. The third compound depicted in the table, N-butyl-idonojirimycin, is discussed above. The fourth compound shown in the table, N-butyl-6-

[1] Figure 6 shows the percentage of BVDV plaques produced by infected cell cultures in the presence of different concentrations of various compounds, including N-nonyl-altrostatin. The legend of Figure 6 appears to contain errors, however, because the open triangles said to represent the N-nonyl-altrostatin data do not appear in the graph. The experimental results obtained for N-nonyl-altrostatin therefore cannot be ascertained from Figure 6.

methyl-galactonojirimycin, has a methyl group substituent at position 2, rather than the $-CH_2OH$ group of the compounds of formula I of the present claims, and is thus not a structural homolog of the claimed compounds. Finally, the first two polyhydroxypiperidines shown in the table, N-butyl-deoxynojirimycin and N-butyl-deoxygalactonojirimycin, are discussed below.

"A *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or surprising properties." M.P.E.P. § 2144.09. For example, in *In re Papesch*[2], affidavit evidence showing that the claimed triethylated compounds possessed anti-inflammatory activity, while prior art trimethylated compounds did not, was sufficient to overcome an obviousness rejection based on the homologous relationship between the prior art and claimed compounds.

As discussed in the response to the Office Action dated August 24, 2004, Applicants have discovered a class of chemical compounds that possess properties that the N-butyl-deoxynojirimycin and N-butyl-deoxygalactonojirimycin compounds described in the Mellor article do not possess. Compounds defined by the present claims are ***specific and selective*** inhibitors of human glucosylceramide synthase (GCS) and do not inhibit human β-galactosidase, human β-glucosidase, and human α-glucosidase. See, for example, paragraphs 92 and 93 of the specification as originally filed. In contrast, N-butyl-deoxynojirimycin (NB-DNJ) and N-butyl-deoxygalactonojirimycin (NB-DGJ), inhibit human β-galactosidase, human β-glucosidase, and human α-glucosidase. Specifically, as shown in Table 2 of the specification, NB-DNJ is a potent inhibitor of human α-glucosidase and also inhibits human β-glucosidase. NB-DGJ is a potent inhibitor of human β-galactosidase. Accordingly, compounds defined by the present claims possess properties that NB-DNJ and NB-DGJ do not possess: they ***selectively*** inhibit human GCS and do not inhibit human β-galactosidase, human β-glucosidase, and human α-glucosidase.

Due to their specific and selective inhibition of GCS, compounds defined by the present claims can be expected to elicit fewer side effects when administered for the treatment of disease states mediated by GCS than would NB-DNJ or NB-DGJ. The selective inhibition of GCS by compounds of formula I, and the expected concomitant reduction in

[2] 137 U.S.P.Q. 43 (C.C.P.A. 1963)

side effects, were not known in the art at the time the invention was made. Accordingly, the subject matter defined by the claims would not have been obvious to those skilled in the art, and Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully Submitted,

Date: 5/9/05

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